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Introduction

Bronchial provocation is often used to diagnose asthma or monitor disease control. Dyspnea perception, however, associates poorly with the induced drop in FEV₁. Some subjects perceive dyspnea well before the drop, while others perceive non. This discrepancy may arise from the origin of dyspnea. As a provocation test solely uses the large airways parameter FEV₁, although dyspnea is associated with both large- and small airways dysfunction.

Aims

We explored if induced **dyspnea perception is equal** for nebulized adenosine 5'-monophosphate (AMP) and dry powder adenosine, targeting large and small airways, respectively. Further we investigated if **dyspnea perception associates** better with large or small airways dysfunction.

Methods

For this study, we used the baseline data of the previously published OLIVIA study¹, in which asthmatics performed an AMP and an adenosine provocation. All 59 subjects performed spirometry, impulse oscillometry (IOS), and Borg dyspnea score, of whom 36 completed a multiple breath nitrogen washout (MBNW). Spearman's correlation analysis was used to associate the change(Δ) in Borg score to the change in large and small airways parameters. To construct a linear multivariate regression model a large and a small airways parameter² was selected (lowest p-value) from spirometry and IOS. MBNW was analyzed separately.

Results

- Provocation with adenosine and AMP evoked a decreases in FEV₁ of 23.4 \pm 8% and 21.1 \pm 8%, respectively. This corresponded with similar levels of induced dyspnea (Figure 1). Δ Borg did not associated with Δ FEV₁ for neither adenosine nor AMP provocation.
- Δ Borg after adenosine provocation associated with a decrease in FEF₂₅ (p=0.01), FEF₇₅ (p<0.01), and FEF₂₅₋₇₅ (p<0.01, Figure 2) and in the multivariate linear regression model (Table 2a) a decrease in FEF₂₅₋₇₅ was independently associated with an increase in Borg.
- Δ Borg after AMP provocation associated univariately with an increased AX (p=0.05) and a decreased X₅ (p=0.04, Figure 3), but in the multivariate analyses no independent associations were found between Δ Borg and any large or small airways parameters (Table 2b).

Table 1: Baseline characteristics

	count or median (IQR)
Gender (M-F)	24 - 35
Age (years)	47.0 (37.0; 55.0)
Smoking (Current-Ex)	30 - 29
Pack-years (years)	16.8 (11.0; 26.0)
Adenosine provocation (mg)	3.11 (0.87; 6.38)
AMP provocation (mg mL ⁻¹)	14.67 (4.7; 44.88)
FEV ₁ (%pred)	85 (74; 96)
FVC (%pred)	105 (94; 116)
FEV ₁ /FVC (%)	70 (62; 77)
FEF ₂₅₋₇₅ (%pred)	49 (35; 65)
R5(kPa sL ⁻¹)	0.53 (0.42; 0.67)
R20 (kPa sL ⁻¹)	0.42 (0.35; 0.47)
AX (kPa L ⁻¹)	0.64 (0.24; 1.82)
X5(kPa sL ⁻¹)	-0.13 (-0.22; -0.09)
LCI5%	6.22 (5.76; 7.37)
Scond	0.04 (0.02; 0.06)
Sacin	0.14 (0.10; 0.19)

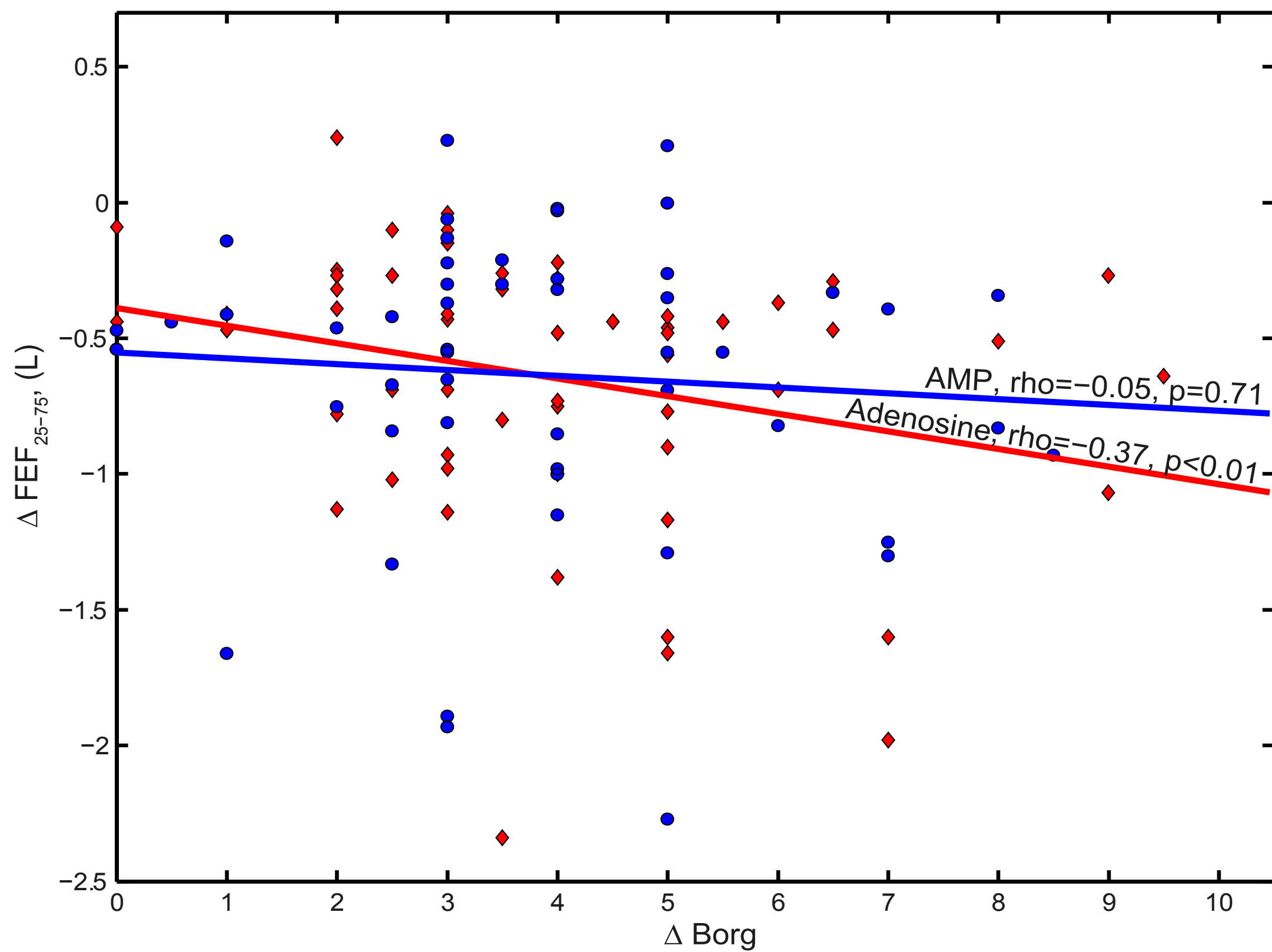


Figure 2: Correlation of change(Δ) in Borg and FEF₂₅₋₇₅.
 Adenosine(♦) induced Δ Borg correlates with Δ FEF₂₅₋₇₅, while AMP(●) induced Δ Borg lacks a correlation.

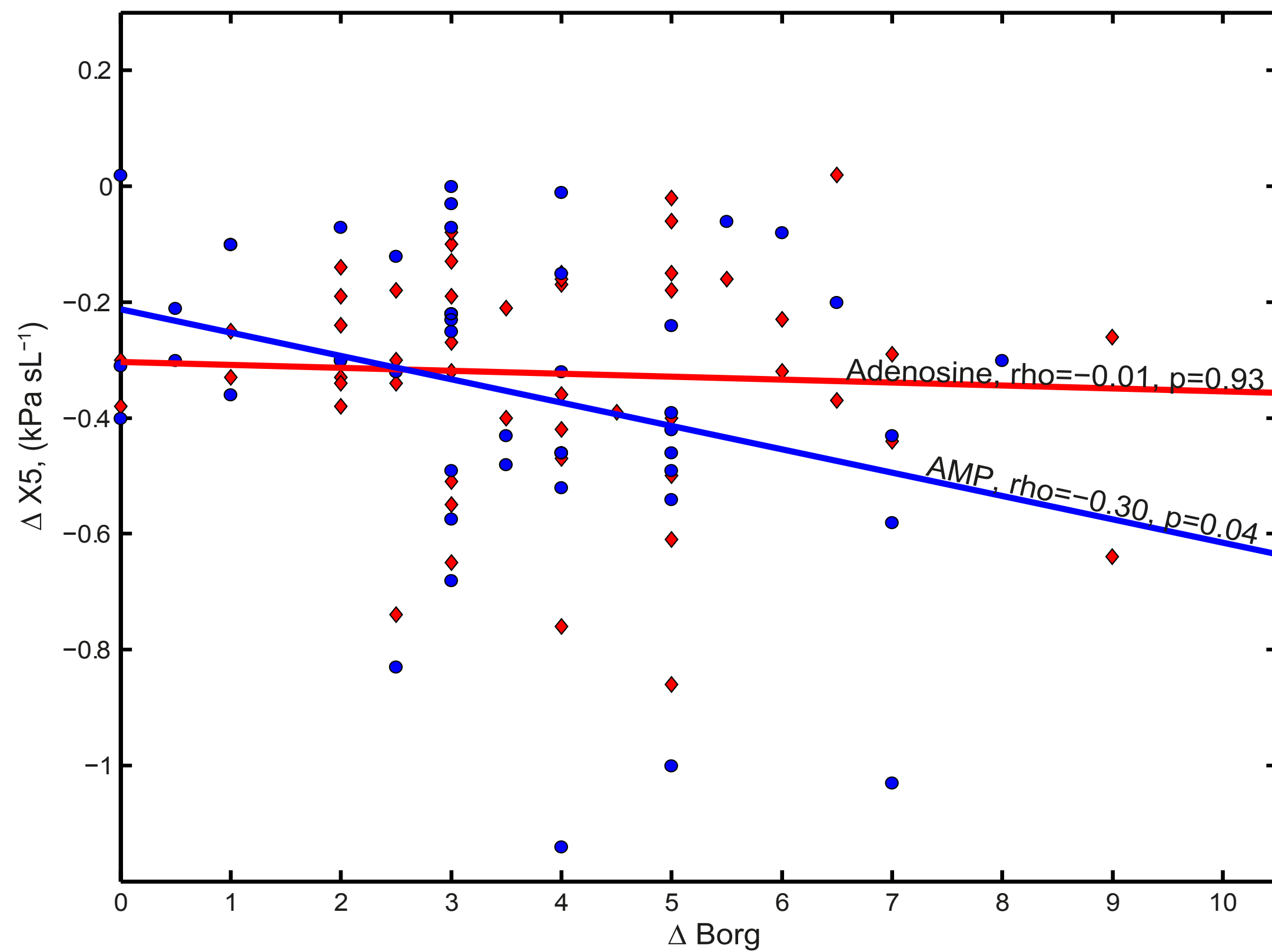


Figure 3: Correlation of change(Δ) in Borg and X₅
 AMP(●) induced Δ Borg correlates with Δ X₅, while adenosine(♦) induced Δ Borg lacks a correlation.

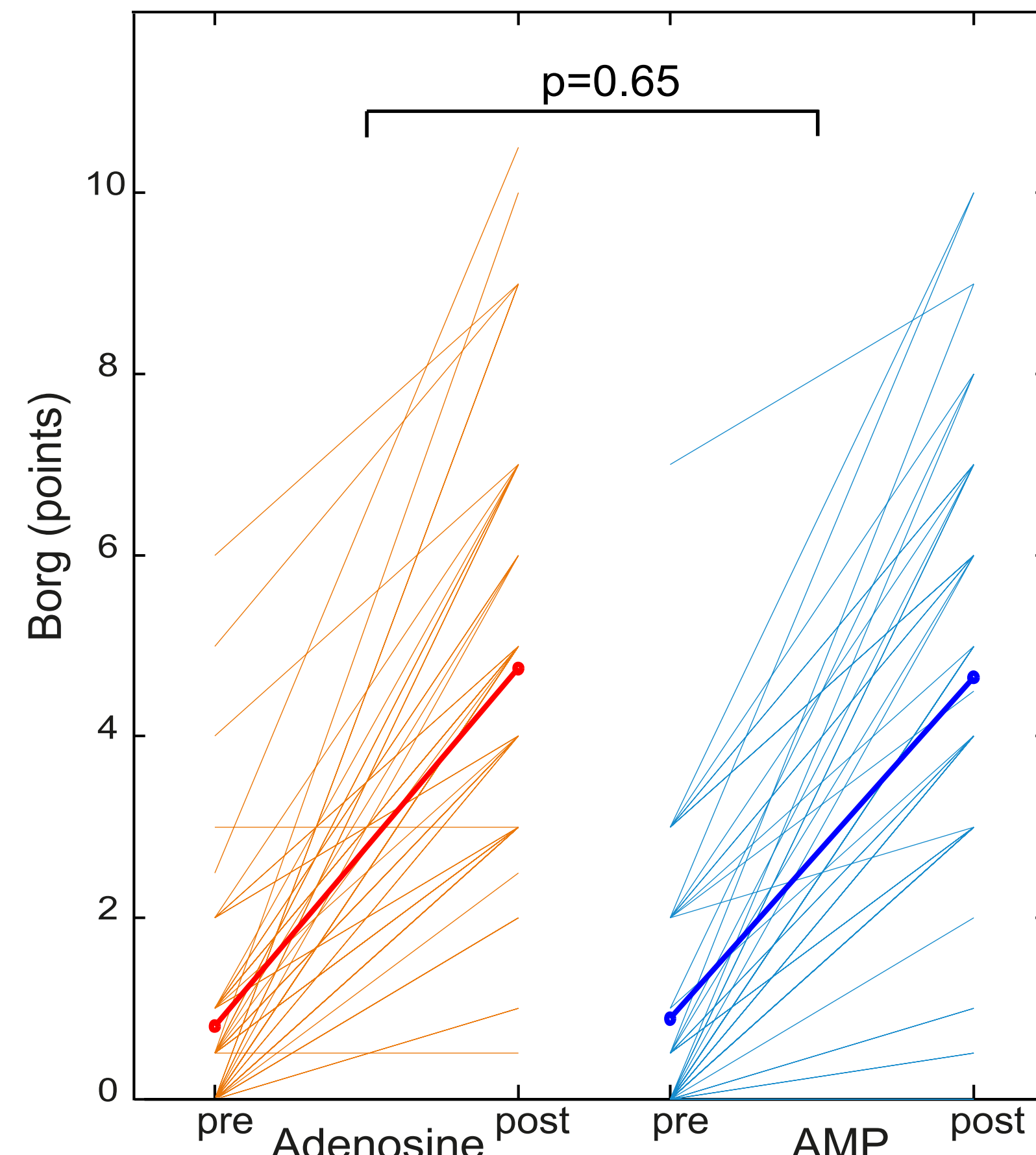


Figure 1: Changes in Borg score (Δ Borg)
 from pre-provocation to post-provocation for adenosine and AMP. Both agents increase dyspnea perception to the same degree.

Table 2: Multivariate models for Δ Borg

	All subjects	MBNW subgroup
A. Adenosine		
	B (p-value)	B (p-value)
Gender	-0.83 (0.37)	-0.81 (0.37)
Smoking status	0.32 (0.65)	0.45 (0.51)
Δ FEV ₁ (L)	1.50 (0.43)	0.98 (0.60)
Δ FEF ₂₅₋₇₅ (Ls ⁻¹)	-2.18 (0.04)	-1.82 (0.09)
Δ R20 (kPa sL ⁻¹)	-8.28 (0.11)	-6.53 (0.20)
Δ R5-R20 (kPa sL ⁻¹)	2.61 (0.27)	3.20 (0.18)
Δ Scond		14.56 (0.16)
B. AMP		
	B (p-value)	B (p-value)
Gender	0.25 (0.78)	0.55 (0.62)
Smoking status	-0.11 (0.90)	-0.23 (0.81)
Δ FEV ₁ (L)	-0.97 (0.62)	-0.74 (0.72)
Δ FEF ₅₀ (Ls ⁻¹)	0.50 (0.54)	0.60 (0.48)
Δ R20 (kPa sL ⁻¹)	-2.00 (0.76)	-1.01 (0.88)
Δ X ₅ (kPa sL ⁻¹)	-0.64 (0.67)	-0.69 (0.65)
Δ LCI5%		0.22 (0.65)

References

- Cox, C. A. et al. Respir. Med. (2017).
- Van Der Wiel, E. J. Allergy Clin. Immunol. (2013).

Conclusions

- AMP and adenosine induce equally severe dyspnea perception.
- Dry powder adenosine-induced dyspnea seems related to small airways involvement independent of the large airways.
- AMP-induced dyspnea associates with neither large nor small airways dysfunction.
- Our results may indicate that dry powder adenosine and nebulized AMP induce dyspnea via different processes.